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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/593,790	MORGAN ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,20,21 and 23-33* is/are pending in the application.

4a) Of the above claim(s) *23-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,20,21 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 15, 20-21, 23-33 are pending.

Applicant's amendment of claims 15, 20-21, addition of claims 29-33, cancellation of claims 17-19, 22, and amendments to the specification as submitted in a communication filed on 7/31/2009 are acknowledged.

This application contains claims 23-28 drawn to a non-elected invention. Claims 15, 20-21, 29-33 are directed to the elected invention and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

1. The specification remains objected to due to the presence of hyperlinks in pages 2, 14 and 41. It is noted that while amendments to the specification have been made, applicant has not deleted the hyperlinks as required by MPEP 608.01. Appropriate correction is required.

2. The specification is objected to for the following reasons. The specification (page 11, lines 10-19) refers to restriction endonucleases such as BcgI and BaeI as type IIG class restriction endonucleases. However, according to Roberts et al. (Nucleic Acid Research 31(7):1805-1812, 2003), BcgI and BaeI are classified as type IIB restriction endonucleases. See page 1809, left column, Type IIB. There is no definition in the specification as to all the species that applicant considers to be type II G restriction endonucleases either so that one could interpret the term "type IIG" as encompassing only those species specifically defined as such in the specification. Therefore, there is an inconsistency between what the

prior art considers a type IIG restriction endonuclease and what the specification appears to consider a type IIG restriction endonuclease. Correction/clarification is required.

Claim Objections

3. Claims 15 and 29 objected to due to the recitation of "obtaining the type II restriction endonuclease with altered recognition sequence specificity" and "obtaining the type IIG restriction endonuclease with altered specificity" They should be amended to recite "obtaining a type II restriction endonuclease …" since there is no previous mention in the claims of a restriction endonuclease with altered recognition sequence specificity. Appropriate correction is required.

4. Claim 15 is objected to due to the recitation of "comprising at least one of an N-terminal domain…and a C-terminal domain for binding….". It should be amended to recite "comprising at least one of an N-terminal…or a C-terminal …." since the term "comprising at least one of" implies that the subunit comprises at least the N-terminal domain for binding…, the C-terminal domain for binding… or both. Appropriate correction is required.

5. Claims 30-33 are objected to due to the recitation of "a method according to claim X". Since the method has been defined in claim X, the claims should be amended to recite "the method according to claim X". Appropriate correction is required.

6. Claims 30-33 are objected to due to the recitation of "comprises: …". The term should read "comprises" without the colon. Appropriate correction is required.

7. Claim 32 is objected to due the fact that it does not end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 15, 20-21, 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

10. Claim 15 (claims 20-21 dependent thereon) is indefinite in the recitation of "(b) altering the specificity subunit of the type IIG restriction endonuclease…changing the spacer region…" in view of the fact that there is no antecedent basis for "the type IIG restriction endonuclease" or "the spacer region". For examination purposes, it will be assumed that the term reads "(b) altering the specificity subunit of the type II restriction endonuclease……changing the spacer". Correction is required.

11. Claim 15 (claims 20-21 dependent thereon) is indefinite in the recitation of "tandemly duplicating the N-terminal or C-terminal domain" because it is unclear as to which N-terminal or C-terminal domain is the phrase referring to. There are several domains in a type II restriction endonuclease as this is an enzyme which comprises a restriction (cleavage) subunit and a methylase subunit as well. Each of these subunits would have an N and C-terminal domain. For examination purposes, it will be assumed that the term reads "tandemly duplicating the N-terminal or C-terminal domains of the specificity subunit which bind a half site of a bipartite recognition sequence". Correction is required.

12. Claims 15 and 32 (claims 20-21 dependent thereon) are indefinite in the recitation of "substituting part or all of the specificity subunit with a corresponding part or all of a specificity subunit from a second type II restriction endonuclease, with a modular structure or from a DNA methylase with a modular structure" for the following reasons. It is unclear how one should interpret the term "with a modular structure or from a DNA methylase with a modular structure" within the context of the claims. Is the term intended to encompass substitution of part/all of the specificity subunit with (a) any modular structure having any function, (b) any DNA methylase, or (c) any domain of a DNA methylase? It is noted that the term "modular structure" can represent any domain of a protein and is not limited to a

specific function. For examination purposes, it will be assumed that the term reads "substituting part or all of the specificity subunit with a corresponding part or all of a specificity subunit from a second type II restriction endonuclease". Correction is required.

13. Claim 15 (claims 20-21 dependent thereon) is indefinite in the recitation of "(iv) mutating the specificity subunit of one or more of the domains…" for the following reasons. As written, it appears that the domains comprise specificity subunits. However, as known in the art and indicated in the specification, specificity subunits comprise domains each recognizing a different half of a bipartite recognition sequence. For examination purposes, it will be assumed that the term reads of "(iv) mutating the N-terminal or C-terminal domains of the specificity subunit which bind a half site of a bipartite recognition sequence; and…". Correction is required.

14. Claim 21 is indefinite in the recitation of "wherein the second type II restriction endonuclease or methyltransferase is selected from the group consisting of a type IIG restriction …. and ….methyltransferase" because there is no antecedent basis for the methyltransferase in claim 15. For examination purposes, no patentable weight will be given to the term "γ-type m^6A methyltransferase". Correction is required.

15. Claims 29 and 21 (claims 30-33 dependent thereon) are indefinite in the recitation of "type IIG restriction endonuclease" for the following reasons. The specification (page 11, lines 10-19) refers to restriction endonucleases such as BcgI and BaeI as type IIG class restriction endonucleases. However, Roberts et al. (Nucleic Acid Research 31(7):1805-1812, 2003) teach that BcgI and BaeI are considered type IIB restriction endonucleases. See page 1809, left column, Type IIB. There is no indication as to all the species that applicant considers as members of the type IIG group. As such, it is unclear what is the intended meaning of the term "type IIG" and what is the intended scope of the claim. For examination purposes, it will be assumed that the term reads "selecting a type II restriction endonuclease...". Correction is required.

16. Claim 29 (claims 30-33 dependent thereon) is indefinite in the recitation of "specificity subunit with an N-terminal …separated by a spacer region encoded by a first gene" because it is unclear if the first gene should encode the specificity subunit or the spacer region. For examination purposes, it will be assumed that the first gene should encode the specificity subunit. Correction is required.

17. Claims 29, 31 and 33 (claims 30, 32 dependent thereon) are indefinite in the recitation of "modifying at least one of the N-terminal domain, the C-terminal domain or the spacer region", "tandemly duplicating the N-terminal or the C-terminal domain", and "mutating one or more of the N-terminal and C-terminal domains" because it is unclear which N-terminal domain or which C-terminal domain is being referred to. There are several domains in a type II restriction endonuclease as this is an enzyme which comprises a restriction (cleavage) subunit and a methylase subunit as well. Each of these subunits would have an N and C-terminal domain. For examination purposes, it will be assumed that the terms read "modifying at least one of the N-terminal domain of the specificity subunit, the C-terminal domain of the specificity subunit, or the spacer region of the specificity subunit", "tandemly duplicating the N-terminal or C-terminal domains of the specificity subunit", and "mutating the N-terminal and/or the C-terminal domains of the specificity subunit". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 15 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s),

at the time the application was filed, had possession of the claimed invention. This is a new matter rejection necessitated by amendment.

Claims 15 and 21 are directed in part to a method which requires altering a type II restriction endonuclease which has a specificity subunit having at least one of an N-terminal domain for binding one half site of a bipartite recognition sequence or a C-terminal domain for binding a second half site of the bipartite recognition sequence. While the Examiner has found support for altering a type II restriction endonuclease which has a specificity subunit having both the N-terminal domain for binding one half site of a bipartite recognition sequence and a C-terminal domain for binding a second half site of the bipartite recognition sequence, the Examiner has not found support in the specification as originally filed for altering a type II restriction endonuclease which has a specificity subunit which only comprise one domain that binds a single half site of a bipartite recognition sequence. It is noted that Example VI provides a type II restriction endonuclease (CspCI) which has a complete specificity subunit (both domains) prior modification. Thus, there is no indication that a method which requires the alteration of a type II restriction endonuclease comprising a specificity subunit that has a single domain for binding one half of a bipartite recognition sequence was within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in response to this Office Action.

Claim Rejections - 35 USC § 102

20. Claims 15, 19-20, 22 were rejected under 35 U.S.C. 102(b) as being anticipated by MacWilliams et al. (The EMBL Journal 15(17):4775-4783, 1996; cited in the specification).

21. Claims 15, 18-22 were rejected under 35 U.S.C. 102(b) as being anticipated by Gubler et al. (The EMBL Journal 11(1):233-240, 1992).

22. Since neither the method of MacWilliams et al. nor the method of Gubler et al. require a type II restriction endonuclease, these rejections are hereby withdrawn.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 15, 20-21, 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kong et al. (J. Mol. Biol. 279:823-832, 1998) in view of MacWilliams et al. (The EMBL Journal 15(17):4775-4783, 1996; cited in the specification), and further in view of Gubler et al. (The EMBL Journal 11(1):233-240, 1992). This is a new rejection necessitated by amendment. Specifically, the claims have been amended to now require alteration of a type II restriction endonuclease.

Kong et al. teach the functional organization of the Bcgl restriction endonuclease. Kong et al. teach that the Bcgl R-M system comprises two subunits which are the A subunit and the B subunit; the A subunit contains the methyltransferase domain at the C-terminus of the subunit and the DNA cleavage domain at the N-terminus of the subunit (page 824, left column, second full paragraph; page 826, right

column, first full paragraph). The B subunit contains the target recognition domain (Abstract, last sentence). Kong et al. teach that the B subunit exhibits a repeat structure similar to that of the type I restriction endonuclease S subunit with two variable regions and two conserved regions, where the variable regions (V1 and V2) are the target recognition domains (page 829 right column-page 830, left column. Kong et al. also teach that the recognition sequences of both BcgI and type I R-M systems are asymmetric bipartite sites with specific segments separated by a no-specific spacer of defined length (page 830, left column, lines 1-7). According to the specification, the catalytic subunit and the specificity subunits are encoded by different genes (page 11, lines 10-16). Kong et al. do not teach a method of modifying BcgI.

MacWilliams et al. teach a method to generate a mutant restriction enzyme with a new DNA binding specificity, wherein the mutant restriction enzyme is obtained by deleting the N-terminal domain of the specificity subunit which recognizes the first half site of the sequence recognized by EcoDXXI as well as the TAEL repeats which are the spacer between the N- and C-terminal domains of the specificity subunit (page 4776, left column, last 9 lines-right column, first 6 lines; Figure 1). EcoDXXI is a type I restriction endonuclease and the specificity and catalytic subunits are encoded by the hsdS and the hsdR/hsdM genes, respectively (page 4775, right column, lines 4-8). MacWilliams et al found that the C-terminal domain of the specificity subunit can completely substitute for the missing N-terminal domain, and also disclose that a similar experiment where the C-terminal domain was deleted, showed that the N-terminal domain can completely substitute for the missing C-terminal domain (Abstract).

Gubler et al. teach a method of obtaining hybrid type I restriction endonucleases with altered DNA binding specificities wherein said hybrid type I restriction endonucleases are the result of exchanging the N-terminal or C-terminal domains of the specificity subunits of the EcoDXX1 and EcoR1241 type I restriction endonucleases (Abstract, Figure 3B) as well as modifying the number of TAEL repeats (page 236, left column, lines 7-15-right column, lines 1-5) which are the spacer between

the N- and C-terminal domains. As indicated above, type I restriction endonucleases have different genes encoding the specificity and catalytic subunits (hsdS, hsdR, and hsdM genes).

Claims 15, 20-21, 29-33 as interpreted are directed in part to a method which comprises (A) selecting a type II restriction endonuclease having a specificity subunit and a catalytic subunit, wherein each subunit is encoded by a different gene, wherein the specificity subunit comprises (1) an N-terminal domain which binds to a half site of a bipartite recognition sequence, (2) a C-terminal domain which binds to a second half site of a bipartite recognition sequence, and (3) a spacer region between (1) and (2), (B) altering the specificity subunit of the type II restriction endonuclease by (1) changing the spacer region by modifying its length, (2) tandemly duplicating the N-terminal or the C-terminal domains of the specificity subunit which bind to half sites of a bipartite recognition sequence, (3) substituting part of the specificity subunit with the corresponding part of another type II restriction endonuclease, or substituting the entire specificity subunit with the specificity subunit of another type II restriction endonuclease, or (4) mutating either the N-terminal or the C-terminal domains of the specificity subunit which bind to half sites of a bipartite recognition sequence, and (C) obtaining a type II restriction endonuclease with altered specificity. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the BcgI restriction endonuclease (type II) of Kong et al., which has been described by Kong et al. as having a specificity subunit whose structural/functional organization is similar to that of type I restriction endonucleases, using the method of MacWilliams et al. or Gubler et al. to create a modified BcgI restriction endonuclease having new specificities. Also, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute part or all of the specificity domain with the corresponding part or all of the specificity domain from another type II restriction endonuclease having the same type of structural configuration with regard to the specificity domain and its recognition site (i.e., bipartite recognition site where the N-terminus of the specificity subunit

recognizes one part of the recognition site and the C-terminus of the specificity subunit recognizes the other part of the recognition site) as BcgI.

A person of ordinary skill in the art is motivated to modify the specificity subunit of the BcgI restriction endonuclease of Kong et al. using the methods of MacWilliams et al. and/or Gubler et al. to expand the range of recognition sites of BcgI since (1) the teachings of MacWilliams et al. and Gubler et al. clearly show that the presence of the domain that recognizes one half of the bipartite DNA binding site is not required to recognize the other half of the bipartite binding site, (2) Gubler et al. teach exchanging the N- and C-terminal domains of the specificity subunits of different type I restriction endonucleases (EcoR124 and EcoDXXI) as well as altering the length of the spacer region to create new specificities, (3) the teachings of MacWilliams and Gubler et al. show that one could mix and match among N-terminal and C-terminal domains of specificity subunits from the same or different restriction endonucleases which have a similar structural/functional arrangement to create new binding specificities, and (4) Kong et al. clearly teach that the specificity subunit (B subunit) of BcgI is structurally/functionally organized just like a type I restriction endonuclease specificity subunit. One of ordinary skill in the art has a reasonable expectation of success at making the recited modifications and alter the DNA binding specificity of BcgI since (a) MacWilliams et al. teach that deletion of one terminal domain of the specificity subunit results in the recognition of a palindromic sequence, thus suggesting that (1) the mutant restriction endonucleases use two truncated specificity subunits for recognition (equivalent to two N-terminal domains linked together, or two C-terminal domains linked together), and (2) the remaining terminal domain can substitute for the missing terminal domain (page 4776, left column, lines 16-24; page 4779, right column, lines 2-13), (b) Gubler et al. teach that one could obtain a hybrid restriction endonuclease with a different recognition site by changing the length of the linker and also by exchanging the N- or C-terminal domains of different restriction enzymes which have a similar structural configuration and a bipartite binding site consisting of two parts, each recognized by the N-terminus or the C-terminus of the specificity subunit,

respectively, and (c) all the modifications made to the type I restriction endonucleases of MacWilliams et al. and Gubler et al. to alter specificity were made in the specificity subunits, which have the same structural/functional arrangement as the specificity subunit of BcgI. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

26. Claims 15, 20-21, 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sears et al. (Nucleic Acids Research 24(18):3590-3592, 1996) as evidenced by Kong et al. (J. Mol. Biol. 279:823-832, 1998) in view of MacWilliams et al. (The EMBL Journal 15(17):4775-4783, 1996; cited in the specification), and further in view of Gubler et al. (The EMBL Journal 11(1):233-240, 1992). This is a new rejection necessitated by amendment. Specifically, the claims have been amended to now require alteration of a type II restriction endonuclease.

The teachings of Kong et al., MacWilliams et al. and Gubler et al. have been discussed above. Neither MacWilliams et al. nor Gubler et al. teach modification of the BaeI restriction endonuclease. Sears et al. teach that BaeI is a restriction endonuclease which is a BcgI-like restriction endonuclease (Abstract). The characteristics/organization of BcgI have been discussed extensively above (Kong et al.). As indicated in the specification, the catalytic subunit and the specificity subunits of BaeI are encoded by different genes (page 11, lines 10-16). Sears et al. do not teach a method for modifying BaeI.

Claims 15, 20-21, 29-33 as interpreted are directed in part to a method which comprises (A) selecting a type II restriction endonuclease having a specificity subunit and a catalytic subunit, wherein each subunit is encoded by a different gene, wherein the specificity subunit comprises (1) an N-terminal domain which binds to a half site of a bipartite recognition sequence, (2) a C-terminal domain which binds to a second half site of a bipartite recognition sequence, and (3) a spacer region between (1) and (2), (B) altering the specificity subunit of the type II restriction endonuclease by (1) changing the spacer

region by modifying its length, (2) tandemly duplicating the N-terminal or the C-terminal domains of the specificity subunit which bind to half sites of a bipartite recognition sequence, (3) substituting part of the specificity subunit with the corresponding part of another type II restriction endonuclease, or substituting the entire specificity subunit with the specificity subunit of another type II restriction endonuclease, or (4) mutating either the N-terminal or the C-terminal domains of the specificity subunit which bind to half sites of a bipartite recognition sequence, and (C) obtaining a type II restriction endonuclease with altered specificity. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the BaeI restriction endonuclease (type II) of Sears et al., which has been described by Sears et al. as being a BcgI-like restriction endonuclease, thus having a specificity subunit whose structural/functional organization is similar to that of type I restriction endonucleases, using the method of MacWilliams et al. or Gubler et al. to create a modified BaeI restriction endonuclease having new specificities. Also, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute part or all of the specificity domain with the corresponding part or all of the specificity domain from another type II restriction endonuclease having the same type of structural configuration with regard to the specificity domain and its recognition site (i.e., bipartite recognition site where the N-terminus of the specificity subunit recognizes one part of the recognition site and the C-terminus of the specificity subunit recognizes the other part of the recognition site) as BaeI.

A person of ordinary skill in the art is motivated to modify the BaeI restriction endonuclease of Sears et al. using the methods of MacWilliams et al. and/or Gubler et al. to expand the range of recognition sites of BaeI since (1) the teachings of MacWilliams et al. and Gubler et al. clearly show that the presence of the domain that recognizes one half of the bipartite DNA binding site is not required to recognize the other half of the bipartite binding site, (2) Gubler et al. teach exchanging the N- and C-terminal domains of the specificity subunits of different type I restriction endonucleases (EcoR124 and

EcoDXXI) as well as altering the length of the spacer region to create new specificities, (3) the teachings of MacWilliams and Gubler et al. show that one could mix and match among N-terminal and C-terminal domains of specificity subunits from the same or different restriction endonucleases which have a similar structural/functional arrangement to create new binding specificities, (4) Sears et al. teach that BaeI is a BcgI-like restriction endonuclease, and (4) Kong et al. clearly teach that the specificity subunit (B subunit) of BcgI is structurally/functionally organized just like a type I restriction endonuclease specificity subunit. One of ordinary skill in the art has a reasonable expectation of success at making the recited modifications and alter the DNA binding specificity of BaeI since (a) MacWilliams et al. teach that deletion of one terminal domain of the specificity subunit results in the recognition of a palindromic sequence, thus suggesting that (1) the mutant restriction endonucleases use two truncated specificity subunits for recognition (equivalent to two N-terminal domains linked together, or two C-terminal domains linked together), and (2) the remaining terminal domain can substitute for the missing terminal domain (page 4776, left column, lines 16-24; page 4779, right column, lines 2-13), (b) Gubler et al. teach that one could obtain a hybrid restriction endonuclease with a different recognition site by changing the length of the spacer and also by exchanging the N- or C-terminal domains of different restriction enzymes which have a similar structural configuration and a bipartite binding site consisting of two parts, each recognized by the N-terminus or the C-terminus of the specificity subunit, respectively, and (c) all the modifications made to the type I restriction endonucleases of MacWilliams et al. and Gubler et al. to alter specificity were made in the specificity subunits, which have the same structural/functional arrangement as the specificity subunit of BaeI. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

27. Claim 17 was rejected under 35 U.S.C. 103(a) as being unpatentable over MacWilliams et al. (The EMBL Journal 15(17):4775-4783, 1996; cited in the specification) in view of Gubler et al. (The EMBL Journal 11(1):233-240, 1992).

28. In view of applicant's cancellation of claim 17, this rejection has been rendered moot and is hereby withdrawn.

29. With regard to the previous art rejections under 35 USC 102(b) and 103(a), applicant argues that the cited references are directed to subject matter which is different from the present claimed invention. Specifically, applicant indicates that the organization of type I restriction endonucleases is significantly different from how type II restriction endonucleases are organized. Applicant states that type I endonucleases are encoded by a transcriptional unit comprising both the specificity domain and the methylase domain and another transcriptional unit comprising a restriction domain, whereas type II endonucleases are encoded by a transcriptional unit that comprises the methylase and restriction domains, and another transcriptional unit which comprises the specificity domain. Applicant also points out differences with regard to how type I and II endonucleases cleave their target and the location of the cleavage site with regard to the recognition site. Furthermore, applicant argues that the dimeric structure of the specificity domain of type I endonucleases is different from the dimeric structure of the specificity domain of CspCI in that the linker region in type I endonucleases is an extended duplex alpha helix region whereas in CspCI, it is a shorter non-homogenous region. Applicant notes that despite publication of the cited art in 1992 and 1996, almost 10 years before the filing of the instant application, no report prior to the present application has been made disclosing the modification of a type IIG endonuclease in the specificity domain.

30. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the structural/functional differences between type I and type II restriction endonucleases. However, it is noted that as taught by Kong et al. and Sears et al.,

BcgI and BaeI have a structural/functional organization which is partly similar to type I restriction endonucleases. Specifically, the specificity domains of BcgI and BaeI appear to be very similar to that found in type I restriction endonucleases, as evidenced by the teachings of Kong et al. It is reiterated herein that the only modifications taught by MacWilliams et al. and Gubler et al. were made in the specificity domain, which is the domain Kong et al. teach as being substantially similar to that found in type I restriction endonucleases. Thus, while not identical in structure to type I endonucleases, at least BcgI and BaeI appear to be restriction endonucleases which share a great deal of similarity in structure to the specificity domains of type I endonucleases. Also, with regard to arguments that the linker region of type I endonucleases is longer and more structured than the linker region of type II endonucleases, it is noted that in both cases, the general structure of the specificity domains remains the same, i.e., an N- and C-terminal domain each recognizing one half site of a bipartite recognition sequence separated by a linker region. In response to applicant's argument based upon the age of the references and how the claimed invention was not disclosed before the filing of the instant application even though the cited references were published in 1992 and 1996, it is noted that an allegation of an unsolved problem is not evidence of unobviousness unless there is shown efforts and failure to solve the problem. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977), *In re Allen*, 324 F.2d 993, 997, 139 USPQ 492, 495 (CCPA 1963). It should also be noted that Rimseliene et al. (J. Mol. Biol. 327:383-391, 2003; previously cited) teach the modification of type II restriction endonucleases (Eco57I) to obtain different specificities by introducing amino acid substitutions in the target recognition domain (page 385, Figure 1, right column, Amino acid substitutions; T862; page 388, left column, first full paragraph). Thus, while using a different method (different modifications), the prior art before applicant's invention, disclosed the modification of the specificity domain to create new specificities.

Conclusion

31. No claim is in condition for allowance.

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

33. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (571) 273-8300. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached at (571) 272-0811. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
December 2, 2009